HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TRILIPIX safely and effectively. See full prescribing information for TRILIPIX.

TRILIPIX (choline fenofibrate) capsule, delayed release for oral use
Initial U.S. Approval: 2008

INDICATIONS AND USAGE

Trilipix is a peroxisome proliferator receptor alpha (PPARα) activator indicated:

- In combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and CHD or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal (1.1).
- As monotherapy to reduce TG in patients with severe hypertriglyceridemia (1.2).
- As monotherapy to reduce elevated LDL-C, Total-C, TG and Apo B, and to increase HDL-C in patients with primary hyperlipidemia or mixed dyslipidemia (1.3).

Limitations of use: No incremental benefit of Trilipix on cardiovascular morbidity and mortality over and above that demonstrated for statin monotherapy has been established.
General Considerations For Treatment: Fenofibrate at a dose equivalent to 135 mg of Trilipix was not shown to reduce coronary heart disease morbidity and mortality in a large, randomized controlled trial of patients with type 2 diabetes mellitus.

DOSAGE AND ADMINISTRATION

- Mixed dyslipidemia: 135 mg once daily (2.2).
- Hypertriglyceridemia: 45 to 135 mg once daily (2.3).
- Renally impaired patients: 45 mg once daily (2.5).
- Maximum dose: 135 mg once daily (2.1).
- May be taken without regard to food (2.1).
- May be taken at the same time as a statin (2.2).
- Co-administration with the maximum dose of a statin has not been evaluated in clinical studies and should be avoided unless the benefits are expected to outweigh the risks (2.2).

DOSAGE FORMS AND STRENGTHS

Oral Delayed Release Capsules: 45 mg and 135 mg (3).

CONTRAINDICATIONS

- Severe renal dysfunction, including patients receiving dialysis (4, 12.3).
- Active liver disease (4, 5.3).
- Gallbladder disease (4, 5.4).
- Nursing mothers (4, 8.3).

WARNINGS AND PRECAUTIONS

- Myopathy and rhabdomyolysis have been reported in patients taking fenofibrate. The risks for myopathy and rhabdomyolysis are increased when fibrates are co-administered with a statin (with a significantly higher rate observed for gemfibrozil), particularly in elderly patients and patients with diabetes, renal failure, or hypothyroidism (5.1).
- Trilipix can increase serum transaminases. Liver tests should be monitored periodically (5.3).
- Trilipix can reversibly increase serum creatinine levels (5.2). Renal function should be monitored periodically in patients with renal insufficiency (8.6).
- Trilipix increases cholesterol excretion into the bile, leading to risk of cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated (5.4).
- Exercise caution in concomitant treatment with oral coumarin anticoagulants. Adjust the dosage of coumarin anticoagulant to maintain the prothrombin time/INR at the desired level to prevent bleeding complications (5.5).

ADVERSE REACTIONS

The most common adverse events (≥ 3% of patients receiving Trilipix or Trilipix co-administered with statins) are headache, back pain, nasopharyngitis, nausea, myalgia, diarrhea, and upper respiratory tract infection (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Abbott Laboratories at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Coumarin Anticoagulants: (7.1).
- Bile Acid Resins: (7.2).
- Cyclosporine: (7.3).

USE IN SPECIFIC POPULATIONS

- Geriatric Use: Dose selection for the elderly should be made on the basis of renal function (8.5).
- Renal Impairment: Trilipix should be avoided in patients with severe renal impairment. Dose adjustment is required in patients with mild to moderate renal impairment (8.6).
- The use of Trilipix has not been evaluated in patients with hepatic impairment (8.7).

See 17 for PATIENT COUNSELING INFORMATION and the FDA-approved Medication Guide

Revised: 12/2008

FULL PRESCRIBING INFORMATION: CONTENTS *

*** Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Co-administration Therapy with Statins for the Treatment of Mixed Dyslipidemia

Trilipix is indicated as an adjunct to diet in combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and CHD or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal.
CHD risk equivalents comprise:

- Other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease);
- Diabetes;
- Multiple risk factors that confer a 10-year risk for CHD > 20%

1.2 Treatment of Severe Hypertriglyceridemia

Trilipix is indicated as adjunctive therapy to diet to reduce TG in patients with severe hypertriglyceridemia. Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually obviate the need for pharmacological intervention. Markedly elevated levels of serum triglycerides (e.g. > 2,000 mg/dL) may increase the risk of developing pancreatitis. The effect of Trilipix therapy on reducing this risk has not been adequately studied.

1.3 Treatment of Primary Hyperlipidemia or Mixed Dyslipidemia

Trilipix is indicated as adjunctive therapy to diet to reduce elevated LDL-C, Total-C, TG, and Apo B, and to increase HDL-C in patients with primary hyperlipidemia or mixed dyslipidemia.

1.4 Important Limitations of Use

No incremental benefit of Trilipix on cardiovascular morbidity and mortality over and above that demonstrated for statin monotherapy has been established.

1.5 General Considerations for Treatment

Fenofibrate at a dose equivalent to 135 mg of Trilipix was not shown to reduce coronary heart disease morbidity and mortality in a large, randomized controlled trial of patients with type 2 diabetes mellitus.

Laboratory studies should be performed to establish that lipid levels are abnormal before instituting Trilipix therapy.

Every reasonable attempt should be made to control serum lipids with non-drug methods including appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that may be contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (beta-blockers, thiazides, estrogens) should be discontinued or changed if possible, and excessive alcohol intake should be addressed before triglyceride-lowering drug therapy is considered. If the decision is made to use lipid-altering drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

Drug therapy is not indicated for patients who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of VLDL.

2 DOSAGE AND ADMINISTRATION

2.1 General Considerations

Patients should be placed on an appropriate lipid-lowering diet before receiving Trilipix as monotherapy or co-administered with a statin *[see DOSAGE AND ADMINISTRATION (2.2, 2.3 and 2.4)]*, and should continue this diet during treatment. Trilipix delayed release capsules can be taken without regard to meals. Serum lipids should be monitored periodically. The maximum dose is 135 mg once daily.

2.2 Co-administration Therapy with Statins for the Treatment of Mixed Dyslipidemia

Trilipix 135 mg may be co-administered with an HMG-CoA reductase inhibitor (statin) in patients with mixed dyslipidemia. For convenience, the daily dose of Trilipix may be taken at the same time as a statin, according to the dosing recommendations for each medication. Co-administration with the maximum dose of a statin has not been evaluated in clinical studies and should be avoided unless the benefits are expected to outweigh the risks.

2.3 Severe Hypertriglyceridemia

The initial dose of Trilipix is 45 to 135 mg once daily. Dosage should be individualized according to patient response, and should be adjusted if necessary following repeat lipid determinations at 4 to 8 week intervals. The maximum dose is 135 mg once daily.

2.4 Primary Hyperlipidemia or Mixed Dyslipidemia

The dose of Trilipix is 135 mg once daily.

2.5 Impaired Renal Function

Treatment with Trilipix should be initiated at a dose of 45 mg once daily in patients with mild to moderate renal impairment and should only be increased after evaluation of the effects on renal function and lipid levels at this dose. The use of Trilipix should be avoided in patients with severely impaired renal function.

2.6 Elderly Patients

Dose selection for the elderly should be made on the basis of renal function *[see USE IN SPECIFIC POPULATIONS (8.5)]*.

3 DOSAGE FORMS AND STRENGTHS

- 45 mg choline fenofibrate delayed release capsules with a reddish-brown cap imprinted in white ink the Abbott “A” logo and a yellow body imprinted in black ink the number “45”.

- 135 mg choline fenofibrate delayed release capsules with a blue cap imprinted in white ink the Abbott “A” logo and a yellow body imprinted in black ink the number “135”.

4 CONTRAINDICATIONS

Trilipix is contraindicated in:

- patients with severe renal impairment, including those receiving dialysis.

- patients with active liver disease, including those with primary biliary cirrhosis and unexplained persistent liver function abnormalities.

- patients with preexisting gallbladder disease.

- nursing mothers.

- patients with hypersensitivity to fenofibric acid, choline fenofibrate or fenofibrate *[see WARNINGS and PRECAUTIONS (5.7)]*.

When Trilipix is co-administered with a statin, refer to the *Contraindications* section of the respective statin labeling.

5 WARNINGS AND PRECAUTIONS

5.1 Skeletal Muscle

Fibrate and statin monotherapy increase the risk of myositis or myopathy, and have been associated with rhabdomyolysis. Data from observational studies suggest that the risk for rhabdomyolysis is increased when fibrates are co-administered with a statin (with a significantly higher rate observed for gemfibrozil). Refer to the respective statin labeling for important drug-drug interactions that increase statin levels and could increase this risk. The risk for serious muscle toxicity appears to be increased in elderly patients and in patients with diabetes, renal failure, or hypothyroidism.

Myalgia was reported in 3.3% of patients treated with Trilipix monotherapy and 3.1% to 3.5% of patients treated with Trilipix co-administered with statins compared to 4.7% to 6.1% of patients treated with statin monotherapy. Increases in creatine phosphokinase (CPK) to > 5 times upper limit of normal occurred in no patients treated with Trilipix monotherapy and 0.2% to 1.2% of patients treated with Trilipix co-administered with statins compared to 0.4% to 1.3% of patients treated with statin monotherapy.

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevations of CPK levels. Patients should promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms, and Trilipix and statin therapy should be discontinued if markedly elevated CPK levels occur or myopathy or myositis is diagnosed.

5.2 Serum Creatinine

Reversible elevations in serum creatinine have been reported in patients receiving Trilipix as monotherapy or co-administered with statins as well as patients receiving fenofibrate. In the pooled analysis of three double-blind controlled studies of Trilipix administered as monotherapy or in combination with statins, increases in creatinine to > 2 mg/dL occurred in 0.8% of patients treated with Trilipix monotherapy and 1.1% to 1.3% of patients treated with Trilipix co-administered with statins compared to 0% to 0.4% of patients treated with statin monotherapy. Elevations in serum creatinine were generally stable over time with no evidence for continued increases in serum creatinine with long-term therapy and tended to return to baseline following discontinuation of treatment. The clinical significance of these observations is unknown. Monitoring renal function in patients with renal impairment taking Trilipix is suggested. Renal monitoring should be considered for patients at risk for renal insufficiency, such as the elderly and those with diabetes.

5.3 Liver Function

Trilipix at a dose of 135 mg once daily administered as monotherapy or co-administered with low to moderate doses of statins has been associated with increases in serum transaminases [AST (SGOT) or ALT (SGPT)]. In a pooled analysis of three double-blind controlled studies of Trilipix administered as monotherapy or in combination with statins, increases to > 3 times the upper limit of normal on two consecutive occasions in ALT and AST occurred in 1.9% and 0.2%, respectively, of patients receiving Trilipix monotherapy and in 1.3% and 0.4%, respectively, of patients receiving Trilipix co-administered with statins. Increases to > 3 times the upper limit of normal in ALT and AST occurred in no patients receiving low- to moderate-dose statin monotherapy. Increases to > 3 times the upper limit of normal in ALT and AST occurred in 0.8% and 0.4%, respectively in patients receiving high-dose statin monotherapy. In a long-term study of Trilipix co-administered with statins for up to 52 weeks, increases of > 3 times the upper limit of normal on two consecutive occasions of ALT and AST occurred in 1.2% and 0.5% of patients, respectively. When transaminase determinations were followed either after discontinuation of treatment or during continued treatment, a return to normal limits was usually observed. Increases in ALT and/or AST were not accompanied by increases in bilirubin or clinically significant increases in alkaline phosphatase.

In a pooled analysis of 10 placebo-controlled trials of fenofibrate, increases to > 3 times the upper limit of normal in ALT occurred in 5.3% of patients taking fenofibrate versus 1.1% of patients treated with placebo. The incidence of increases in transaminases observed with fenofibrate therapy may be dose related. In an 8-week dose-ranging study of fenofibrate in hypertriglyceridemia, the incidence of ALT or AST elevations ≥ 3 times the upper limit of normal was 13% in patients receiving dosages equivalent to 90 mg to 135 mg Trilipix once daily and was 0% in those receiving dosages equivalent to 45 mg Trilipix once daily or less, or placebo. Hepatocellular, chronic active, and cholestatic hepatitis observed with fenofibrate therapy have been reported after exposures of weeks to several years. In extremely rare cases, cirrhosis has been reported in association with chronic active hepatitis.

Regular monitoring of liver function, including serum ALT (SGPT) should be performed for the duration of therapy with Trilipix, and therapy discontinued if enzyme levels persist above 3 times the upper limit of normal.

5.4 Cholelithiasis

Trilipix, like fenofibrate, clofibrate, and gemfibrozil, may increase cholesterol excretion into the bile, potentially leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Trilipix therapy should be discontinued if gallstones are found.

5.5 Concomitant Oral Anticoagulants
Caution should be exercised when Trilipix is given in conjunction with oral coumarin anticoagulants. Trilipix may potentiate the anticoagulant effects of these agents resulting in prolongation of the prothrombin time/INR. Frequent monitoring of prothrombin time/ INR and dose adjustment of the oral anticoagulant are recommended until the prothrombin time/INR has stabilized in order to prevent bleeding complications.

5.6 Pancreatitis
Pancreatitis has been reported in patients taking drugs of the fibrate class, including Trilipix. This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct.

5.7 Hypersensitivity Reactions
Acute hypersensitivity reactions including severe skin rashes requiring patient hospitalization and treatment with steroids have occurred very rarely during treatment with fenofibrate, including rare spontaneous reports of Stevens-Johnson Syndrome and toxic epidermal necrolysis.

5.8 Hematological Changes
Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been observed in patients following initiation of Trilipix and fenofibrate therapy. Extremely rare spontaneous reports of thrombocytopenia and agranulocytosis have been received with fenofibrate therapy.

5.9 Mortality and Coronary Heart Disease Morbidity
The effect of Trilipix on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established. Because of similarities between Trilipix and fenofibrate, clofibrate, and gemfibrozil, the findings in the following large randomized, placebo-controlled clinical studies with these fibrate drugs may also apply to Trilipix.
The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was a 5-year randomized, placebo-controlled study of 9795 patients with type 2 diabetes mellitus treated with fenofibrate. Fenofibrate demonstrated a non-significant 11% relative reduction in the primary outcome of coronary heart disease events (hazard ratio [HR] 0.89, 95% CI 0.75-1.05, p = 0.16) and a significant 11% reduction in the secondary outcome of total cardiovascular disease events (HR 0.89 [0.80-0.99], p = 0.04). There was a non-significant 11% (HR 1.11 [0.95, 1.29], p = 0.18) and 19% (HR 1.19 [0.90, 1.57], p = 0.22) increase in total and coronary heart disease mortality, respectively, with fenofibrate as compared to placebo.
In the Coronary Drug Project, a large study of post-myocardial infarction patients treated for 5 years with clofibrate, there was no difference in mortality seen between the clofibrate group and the placebo group. There was, however, a difference in the rate of cholelithiasis and cholecystitis requiring surgery between the two groups (3.0% vs. 1.8%).
In a study conducted by the World Health Organization (WHO), 5000 subjects without known coronary artery disease were treated with placebo or clofibrate for 5 years and followed for an additional one year. There was a statistically significant, higher age-adjusted all-cause mortality in the clofibrate group compared with the placebo group (5.70% vs. 3.96%, p = < 0.01). Excess mortality was due to a 33% increase in non-cardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. This appeared to confirm the higher risk of gallbladder disease seen in clofibrate-treated patients studied in the Coronary Drug Project.
The Helsinki Heart Study was a large (N = 4081) study of middle-aged men without a history of coronary artery disease. Subjects received either placebo or gemfibrozil for 5 years, with a 3.5 year open extension afterward. Total mortality was numerically higher in the gemfibrozil randomization group but did not achieve statistical significance (p = 0.19, 95% confidence interval for relative risk G:P = 0.91-1.64). Although cancer deaths trended higher in the gemfibrozil group (p = 0.11), cancers (excluding basal cell carcinoma) were diagnosed with equal frequency in both study groups. Due to the limited size of the study, the relative risk of death from any cause was not shown to be different than that seen in the 9 year follow-up data from WHO study (RR = 1.29). A secondary prevention component of the Helsinki Heart Study enrolled middle-aged men excluded from the primary prevention study because of known or suspected coronary heart disease. Subjects received gemfibrozil or placebo for 5 years. Although cardiac deaths trended higher in the gemfibrozil group, this was not statistically significant (hazard ratio 2.2, 95% confidence interval: 0.94-5.05).

5.10 Venothromboembolic Disease
In the FIELD trial, pulmonary embolus (PE) and deep vein thrombosis (DVT) were observed at higher rates in the fenofibrate- than the placebo-treated group. Of 9,795 patients enrolled in FIELD, there were 4,900 in the placebo group and 4,895 in the fenofibrate group. For DVT, there were 48 events (1%) in the placebo group and 67 (1%) in the fenofibrate group (p = 0.074); and for PE, there were 32 (0.7%) events in the placebo group and 53 (1%) in the fenofibrate group (p = 0.022).
In the Coronary Drug Project, a higher proportion of the clofibrate group experienced definite or suspected fatal or nonfatal PE or thrombophlebitis than the placebo group (5.2% vs. 3.3% at five years; p < 0.01).

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse event rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug.

Trilipix (fenofibric acid)

Monotherapy

Treatment-emergent adverse events reported in 3% or more of patients treated with Trilipix during the randomized controlled trials are listed in Table 1 below.

Co-Administration Therapy with Statins (Double-blind Controlled Trials)

Treatment-emergent adverse events reported in 3% or more of patients treated with Trilipix co-administered with statins during the randomized controlled trials are listed in Table 1 below.

Table 1. Treatment-Emergent Adverse Events Reported in ≥ 3% of Patients Receiving Trilipix or Trilipix Co-Administered with a Statin During Double-Blind Controlled Studies [Number (%)]

Adverse Event	Trilipix (N = 490)	Low-Dose Statin (N = 493)	Trilipix + Low-Dose Statin (N = 490)	Moderate-Dose Statin (N = 491)	Trilipix + Moderate-Dose Statin (N = 489)	High-Dose Statin (N = 245)
Gastrointestinal Disorders						
Constipation	16 (3.3)	11 (2.2)	16 (3.3)	13 (2.6)	15 (3.1)	6 (2.4)
Diarrhea	19 (3.9)	16 (3.2)	15 (3.1)	24 (4.9)	18 (3.7)	17 (6.9)
Dyspepsia	18 (3.7)	13 (2.6)	13 (2.7)	17 (3.5)	23 (4.7)	6 (2.4)
Nausea	21 (4.3)	18 (3.7)	17 (3.5)	22 (4.5)	27 (5.5)	10 (4.1)
General Disorders and Administration Site Conditions						
Fatigue	10 (2.0)	13 (2.6)	13 (2.7)	13 (2.6)	16 (3.3)	5 (2.0)
Pain	17 (3.5)	9 (1.8)	16 (3.3)	8 (1.6)	7 (1.4)	8 (3.3)
Infections and Infestations						
Nasopharyngitis						
Sinusitis	17 (3.5)	29 (5.9)	23 (4.7)	16 (3.3)	21 (4.3)	9 (3.7)
Upper Respiratory	16 (3.3)	4 (0.8)	14 (2.9)	8 (1.6)	17 (3.5)	4 (1.6)
Tract Infection	26 (5.3)	13 (2.6)	18 (3.7)	23 (4.7)	23 (4.7)	7 (2.9)
Investigations						
ALT Increased	6 (1.2)	2 (0.4)	15 (3.1)	2 (0.4)	12 (2.5)	4 (1.6)
Musculoskeletal and Connective Tissue Disorders						
Arthralgia						
Back Pain	19 (3.9)	22 (4.5)	21 (4.3)	21 (4.3)	17 (3.5)	12 (4.9)
Muscle Spasms	31 (6.3)	31 (6.3)	30 (6.1)	32 (6.5)	20 (4.1)	8 (3.3)
Myalgia	8 (1.6)	18 (3.7)	12 (2.4)	24 (4.9)	15 (3.1)	6 (2.4)
Pain in	16 (3.3)	24 (4.9)	17 (3.5)	23 (4.7)	15 (3.1)	15 (6.1)
Extremity	22 (4.5)	24 (4.9)	14 (2.9)	21 (4.3)	13 (2.7)	9 (3.7)
Nervous System Disorders						
Dizziness	20 (4.1)	8 (1.6)	19 (3.9)	11 (2.2)	16 (3.3)	2 (0.8)
Headache	62 (12.7)	64 (13.0)	64 (13.1)	82 (16.7)	58 (11.9)	32 (13.1)

Low-dose statin = rosuvastatin 10 mg, simvastatin 20 mg, or atorvastatin 20 mg
Moderate-dose statin = rosuvastatin 20 mg, simvastatin 40 mg, or atorvastatin 40 mg
High-dose statin = rosuvastatin 40 mg, simvastatin 80 mg, or atorvastatin 80 mg

Co-Administration Therapy with Statins (Long-Term Exposure for up to 64 Weeks)

Patients successfully completing any one of the three double-blind, controlled studies were eligible to participate in a 52-week long-term extension study where they received Trilipix co-administered with the moderate dose statin. A total of 2201 patients received at least one dose of Trilipix co-administered with a statin in the double-blind controlled study or the long-term extension study for up to a total of 64 weeks of treatment. Additional treatment-emergent adverse events (not listed in Table 1 above) reported in 3% or more of patients receiving Trilipix co-administered with a statin in either the double-blind controlled studies or the long-term extension study are provided below.

Infections and Infestations

Bronchitis, influenza, and urinary tract infection.

Investigations

AST increased, blood CPK increased, and hepatic enzyme increased.

Musculoskeletal and Connective Tissue Disorders

Musculoskeletal pain.

Psychiatric Disorders

Insomnia.

Respiratory, Thoracic, and Mediastinal Disorders

Cough and pharyngolaryngeal pain.

Vascular Disorders

Hypertension.

Fenofibrate

Fenofibric acid is the active metabolite of fenofibrate. Adverse events reported by 2% or more of patients treated with fenofibrate and greater than placebo during double-blind, placebo-controlled trials are listed in Table 2. Adverse events led to discontinuation of treatment in 5.0% of patients treated with fenofibrate and in 3.0% treated with placebo. Increases in liver tests were the most frequent events, causing discontinuation of fenofibrate treatment in 1.6% of patients in double-blind trials.

Table 2. Adverse Events Reported by 2% or More of Patients Treated with Fenofibrate and Greater than Placebo During the Double-Blind, Placebo-Controlled Trials

BODY SYSTEM **Adverse Event**	**Fenofibrate*** **(N = 439)**	**Placebo** **(N = 365)**
BODY AS A WHOLE		
Abdominal Pain	4.6%	4.4%
Back Pain	3.4%	2.5%
Headache	3.2%	2.7%
DIGESTIVE		
Nausea	2.3%	1.9%
Constipation	2.1%	1.4%
INVESTIGATIONS		
Abnormal Liver Tests	7.5%	1.4%
Increased AST	3.4%	0.5%
Increased ALT	3.0%	1.6%
Increased Creatine Phosphokinase	3.0%	1.4%
RESPIRATORY		
Respiratory Disorder	6.2%	5.5%
Rhinitis	2.3%	1.1%

* Dosage equivalent to 135 mg Trilipix

The following adverse events have been identified during postapproval use of fenofibrate: myalgia, rhabdomyolysis, increased creatine phosphokinase, pancreatitis, increased alanine aminotransaminase, increased aspartate aminotransaminase, renal failure, muscle spasms, acute renal failure, hepatitis, cirrhosis, nausea, abdominal pain, anemia, headache, arthralgia, and asthenia. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a casual relationship to drug exposure.

7 DRUG INTERACTIONS

7.1 Oral Anticoagulants

Caution should be exercised when oral coumarin anticoagulants are given in conjunction with Trilipix *[see WARNINGS AND PRECAUTIONS (5.5)]*.

7.2 Bile Acid Resins
Since bile acid resins may bind other drugs given concurrently, patients should take Trilipix at least 1 hour before or 4-6 hours after a bile acid resin to avoid impeding its absorption.

7.3 Cyclosporine
Because cyclosporine can produce nephrotoxicity with decreases in creatinine clearance and rises in serum creatinine, and because renal excretion is the primary elimination route of drugs of the fibrate class including Trilipix, there is a risk that an interaction will lead to decline of renal function. The benefits and risks of using Trilipix with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dose employed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Category: C
The safety of Trilipix in pregnant women has not been established. There are no adequate and well controlled studies of Trilipix in pregnant women. Trilipix should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
When Trilipix is administered with a statin in a woman of childbearing potential, refer to pregnancy category and product labeling for the statin *[see Precautions, Pregnancy]*. All statins are contraindicated in pregnant women.
In pregnant rats given oral dietary doses of 14, 127, and 361 mg/kg/day from gestation day 6-15 during the period of organogenesis, adverse developmental findings were not observed at 14 mg/kg/day (less than 1 times the maximum recommended human dose [MRHD], based on body surface area comparisons; mg/m^2). At higher multiples of human doses evidence of maternal toxicity was observed.
In pregnant rabbits given oral gavage doses of 15, 150, and 300 mg/kg/day from gestation day 6-18 during the period of organogenesis and allowed to deliver, aborted litters were observed at 150 mg/kg/day (10 times the MRHD, based on body surface area comparisons; mg/m^2). No developmental findings were observed at 15 mg/kg/day (at less than 1 times the MRHD, based on body surface area comparisons; mg/m^2).
In pregnant rats given oral dietary doses of 15, 75, and 300 mg/kg/day from gestation day 15 through lactation day 21 (weaning), maternal toxicity was observed at less than 1 times the MRHD, based on body surface area comparisons; mg/m^2.

8.3 Nursing Mothers
Trilipix should not be used in nursing mothers. A decision should be made whether to discontinue nursing or to discontinue the drug.

8.4 Pediatric Use
The safety and effectiveness of Trilipix monotherapy or co-administration with a statin in pediatric patients have not been established.

8.5 Geriatric Use
Trilipix is substantially excreted by the kidney as fenofibric acid and fenofibric acid glucuronide, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Since elderly patients have a higher incidence of renal impairment, the dose selection for the elderly should be made on the basis of renal function *[see CLINICAL PHARMACOLOGY (12.3)]*. Consider monitoring renal function in elderly patients taking Trilipix.

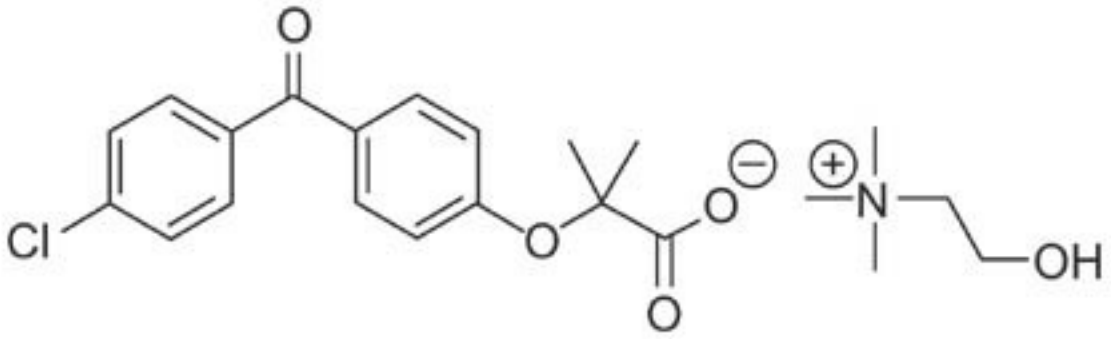
8.6 Renal Impairment
The use of Trilipix should be avoided in patients who have severe renal impairment. Dose reduction is required in patients with mild to moderate renal impairment *[see CLINICAL PHARMACOLOGY (12.3) and DOSAGE AND ADMINISTRATION (2.5)]*. Monitoring renal function in patients with renal impairment is recommended.

8.7 Hepatic Impairment
The use of Trilipix has not been evaluated in subjects with hepatic impairment *[see CONTRAINDICATIONS (4) and CLINICAL PHARMACOLOGY (12.3)]*.

10 OVERDOSAGE
There is no specific treatment for overdose with Trilipix. General supportive care of the patient is indicated, including monitoring of vital signs and observation of clinical status, should an overdose occur. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. Because Trilipix is highly bound to plasma proteins, hemodialysis should not be considered.

11 DESCRIPTION
Trilipix (fenofibric acid) is a lipid regulating agent available as delayed release capsules for oral administration. Each delayed release capsule contains choline fenofibrate, equivalent to 45 mg or 135 mg of fenofibric acid. The chemical name for choline fenofibrate is

ethanaminium, 2-hydroxy-N,N,N-trimethyl, 2-{4-(4-chlorobenzoyl)phenoxy] -2-methylpropanoate (1:1) with the following structural formula:



The empirical formula is $C_{22}H_{28}ClNO_5$ and the molecular weight is 421.91. Choline fenofibrate is freely soluble in water. The melting point is approximately 210°C. Choline fenofibrate is a white to yellow powder, which is stable under ordinary conditions. Each delayed release capsule contains enteric coated mini-tablets comprised of choline fenofibrate and the following inactive ingredients: hypromellose, povidone, water, hydroxylpropyl cellulose, colloidal silicon dioxide, sodium stearyl fumarate, methacrylic acid copolymer, talc, triethyl citrate. The capsule shell of the 45 mg capsule contains the following inactive ingredients: gelatin, titanium dioxide, yellow iron oxide, black iron oxide, and red iron oxide. The capsule shell of the 135 mg capsule contains the following inactive ingredients: gelatin, titanium dioxide, yellow iron oxide, and FD&C Blue #2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The active moiety of Trilipix is fenofibric acid. The pharmacological effects of fenofibric acid in both animals and humans have been extensively studied through oral administration of fenofibrate.

The lipid-modifying effects of fenofibric acid seen in clinical practice have been explained *in vivo* in transgenic mice and *in vitro* in human hepatocyte cultures by the activation of peroxisome proliferator activated receptor α (PPARα). Through this mechanism, fenofibric acid increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of Apo CIII (an inhibitor of lipoprotein lipase activity).

The resulting decrease in TG produces an alteration in the size and composition of LDL from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation), to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of PPARα also induces an increase in the synthesis of HDL-C and Apo AI and AII.

12.2 Pharmacodynamics

Elevated levels of Total-C, LDL-C, and Apo B, and decreased levels of HDL-C and its transport complex, Apo AI and Apo AII, are risk factors for human atherosclerosis. Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the levels of Total-C, LDL-C, and TG, and inversely with the level of HDL-C. The independent effect of raising HDL-C or lowering TG on the risk of cardiovascular morbidity and mortality has not been determined.

12.3 Pharmacokinetics

Trilipix contains fenofibric acid, which is the only circulating pharmacologically active moiety in plasma after oral administration of Trilipix. Fenofibric acid is also the circulating pharmacologically active moiety in plasma after oral administration of fenofibrate, the ester of fenofibric acid.

Plasma concentrations of fenofibric acid after administration of one 135 mg Trilipix delayed release capsule are equivalent to those after one 200 mg capsule of micronized fenofibrate administered under fed conditions.

Absorption

Fenofibric acid is well absorbed throughout the gastrointestinal tract. The absolute bioavailability of fenofibric acid is approximately 81%.

Peak plasma levels of fenofibric acid occur within 4 to 5 hours after a single dose administration of Trilipix capsule under fasting conditions.

Fenofibric acid exposure in plasma, as measured by C_{max} and AUC, is not significantly different when a single 135 mg dose of Trilipix is administered under fasting or nonfasting conditions.

Distribution

Upon multiple dosing of Trilipix, fenofibric acid levels reach steady state within 8 days. Plasma concentrations of fenofibric acid at steady state are approximately slightly more than double those following a single dose. Serum protein binding is approximately 99% in normal and dyslipidemic subjects.

Metabolism

Fenofibric acid is primarily conjugated with glucuronic acid and then excreted in urine. A small amount of fenofibric acid is reduced at the carbonyl moiety to a benzhydrol metabolite which is, in turn, conjugated with glucuronic acid and excreted in urine.
In vivo metabolism data after fenofibrate administration indicate that fenofibric acid does not undergo oxidative metabolism (e.g., cytochrome P450) to a significant extent.

Excretion

After absorption, Trilipix is primarily excreted in the urine in the form of fenofibric acid and fenofibric acid glucuronide. Fenofibric acid is eliminated with a half-life of approximately 20 hours, allowing once daily administration of Trilipix.

Specific Populations

Geriatrics

In five elderly volunteers 77 to 87 years of age, the oral clearance of fenofibric acid following a single oral dose of fenofibrate was 1.2 L/h, which compares to 1.1 L/h in young adults. This indicates that an equivalent dose of Trilipix can be used in elderly subjects with normal renal function, without increasing accumulation of the drug or metabolites *[see USE IN SPECIFIC POPULATIONS (8.5)]*.

Pediatrics

Trilipix has not been investigated in adequate and well-controlled trials in pediatric patients.

Gender

No pharmacokinetic difference between males and females has been observed for Trilipix.

Race

The influence of race on the pharmacokinetics of Trilipix has not been studied.

Renal Impairment

The pharmacokinetics of fenofibric acid was examined in patients with mild, moderate, and severe renal impairment. Patients with severe renal impairment (creatinine clearance [CrCl] < 30 mL/min showed a 2.7-fold increase in exposure for fenofibric acid and increased accumulation of fenofibric acid during chronic dosing compared to that of healthy subjects. Patients with mild to moderate renal impairment (CrCl 30-80 mL/min) had similar exposure but an increase in the half-life for fenofibric acid compared to that of healthy subjects. Based on these findings, the use of Trilipix should be avoided in patients who have severe renal impairment and dose reduction is required in patients having mild to moderate renal impairment.

Hepatic Impairment

No pharmacokinetic studies have been conducted in patients with hepatic impairment.

Drug-drug Interactions

In vitro studies using human liver microsomes indicate that fenofibric acid is not an inhibitor of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. It is a weak inhibitor of CYP2C8, CYP2C19, and CYP2A6, and mild-to-moderate inhibitor of CYP2C9 at therapeutic concentrations.

Table 3 describes the effects of co-administered drugs on fenofibric acid systemic exposure. Table 4 describes the effects of co-administered fenofibric acid on other drugs.

Table 3. Effects of Co-Administered Drugs on Fenofibric Acid Systemic Exposure from Trilipix or Fenofibrate Administration

Co-Administered Drug	Dosage Regimen of Co-Administered Drug	Dosage Regimen of Trilipix or Fenofibrate	Changes in Fenofibric Acid Exposure	
			AUC	C_{max}
No dosing adjustment required for Trilipix with the following co-administered drugs				
Lipid-lowering agents				
Rosuvastatin	40 mg QD for 10 days	Trilipix 135 mg QD for 10 days	↓2%	↓2%
Atorvastatin	20 mg QD for 10 days	Fenofibrate 160 mg[1] QD for 10 days	↓2%	↓4%
Pravastatin	40 mg as a single dose	Fenofibrate 3 x 67 mg[2] as a single dose	↓1%	↓2%
Fluvastatin	40 mg as a single dose	Fenofibrate 160 mg[1] as a single dose	↓2%	↓10%
Simvastatin	80 mg QD for 7 days	Fenofibrate 160 mg[1] QD for 7 days	↓5%	↓11%
Ezetimibe	10 mg QD for 10 days	Fenofibrate 145 mg[1] QD for 10 days	0%	↑3%
Anti-diabetic agents				
Glimepiride	1 mg as a single dose	Fenofibrate 145 mg[1] QD for 10 days	↑1%	↓1%

Metformin	850 mg TID for 10 days	Fenofibrate 54 mg[1] TID for 10 days	↓9%	↓6%
Rosiglitazone	8 mg QD for 5 days	Fenofibrate 145 mg[1] QD for 14 days	↑10%	↑3%
Gastrointestinal agents				
Omeprazole	40 mg QD for 5 days	Trilipix 135 mg as a single dose fasting	↑6%	↑17%
Omeprazole	40 mg QD for 5 days	Trilipix 135 mg as a single dose with food	↑4%	↓2%

[1] TriCor (fenofibrate) oral tablet

[2] TriCor (fenofibrate) oral micronized capsule

Table 4. Effects of Trilipix or Fenofibrate Co-Administration on Systemic Exposure of Other Drugs

Dosage Regimen of Trilipix or Fenofibrate	Dosage Regimen of Co-Administered Drug	Change in Co-Administered Drug Exposure		
		Analyte	AUC	C_{max}
No dosing adjustments required for these co-administered drugs with Trilipix				
Lipid-lowering agents				
Trilipix 135 mg QD for 10 days	Rosuvastatin, 40 mg QD for 10 days	Rosuvastatin	↑6%	↑20%
Fenofibrate 160 mg[1] QD for 10 days	Atorvastatin, 20 mg QD for 10 days	Atorvastatin	↓17%	0%
Fenofibrate 3 x 67 mg[2] as a single dose	Pravastatin, 40 mg as a single dose	Pravastatin	↑13%	↑13%
		3α-Hydroxyl-iso-pravastatin	↑26%	↑29%
Fenofibrate 160 mg[1] QD for 10 days	Pravastatin, 40 mg QD for 10 days	Pravastatin	↑28%	↑36%
		3α-Hydroxyl-iso-pravastatin	↑39%	↑55%
Fenofibrate 160 mg[1] as a single dose	Fluvastatin, 40 mg as a single dose	(+)-3R, 5S-Fluvastatin	↑15%	↑16%
Fenofibrate 160 mg[1] QD for 7 days	Simvastatin, 80 mg QD for 7 days	Simvastatin acid	↓36%	↓11%
		Simvastatin	↓11%	↓17%
		Active HMG-CoA Inhibitors	↓12%	↓1%
		Total HMG-CoA Inhibitors	↓8%	↓10%
Fenofibrate 145 mg[1] QD for 10 days	Ezetimibe, 10 mg QD for 10 days	Total Ezetimibe	↑43%	↑33%
		Free Ezetimibe	↑3%	↑11%
		Ezetimibe Glucuronide	↑49%	↑34%
Anti-diabetic agents				
Fenofibrate 145 mg[1] QD for 10 days	Glimepiride, 1 mg as a single dose	Glimepiride	↑35%	↑18%
Fenofibrate 54 mg[1] TID for 10 days	Metformin, 850 mg TID for 10 days	Metformin	↑3%	↑6%
Fenofibrate 145 mg[1] QD for 14 days	Rosiglitazone, 8 mg QD for 5 days	Rosiglitazone	↑6%	↓1%

[1] TriCor (fenofibrate) oral tablet

[2] TriCor (fenofibrate) oral micronized capsule

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13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Trilipix (fenofibric acid)

No carcinogenicity and fertility studies have been conducted with choline fenofibrate or fenofibric acid. However, because fenofibrate is rapidly converted to its active metabolite, fenofibric acid, either during or immediately following absorption both in animals and humans, studies conducted with fenofibrate are relevant for the assessment of the toxicity profile of fenofibric acid. A similar toxicity spectrum is expected after treatment with either Trilipix or fenofibrate.

Fenofibrate

Two dietary carcinogenicity studies have been conducted in rats with fenofibrate. In the first 24-month study, rats were dosed with fenofibrate at 10, 45, and 200 mg/kg/day, approximately 0.3, 1, and 6 times the maximum recommended human dose (MRHD), based on body surface area comparisons (mg/m^2). At a dose of 200 mg/kg/day (6 times the MRHD), the incidence of liver carcinomas was significantly increased in both sexes. A statistically significant increase in pancreatic carcinomas was observed in males at 1 and 6 times the MRHD; an increase in pancreatic adenomas and benign testicular interstitial cell tumors was observed at 6 times the MRHD in males.

A 117-week carcinogenicity study was conducted in rats comparing three drugs: fenofibrate 10 and 60 mg/kg/day (0.3 and 2 times the MRHD), clofibrate (400 mg/kg/day; 2 times the human dose), and gemfibrozil (250 mg/kg/day; 2 times the human dose, based on mg/m^2 surface area). Fenofibrate increased pancreatic acinar adenomas in both sexes and testicular interstitial cell tumors in males at 2 times the MRHD. Clofibrate increased hepatocellular carcinoma and pancreatic acinar adenomas in males and hepatic neoplastic nodules in females. Gemfibrozil increased hepatic neoplastic nodules in males and females, while all three drugs increased testicular interstitial cell tumors in males.

In an 80-week study in mice, fenofibrate 10, 45, and 200 mg/kg/day (approximately 0.2, 1, and 3 times the MRHD on the basis of mg/m^2 surface area) significantly increased the liver carcinomas in both sexes at 3 times the MRHD. In a second 93-week study at 10, 60, and 200 mg/kg/day, fenofibrate significantly increased the liver carcinomas in male and female mice at 3 times the MRHD.

Electron microscopy studies have demonstrated peroxisomal proliferation following fenofibrate administration to the rat. An adequate study to test for peroxisome proliferation in humans has not been done, but changes in peroxisome morphology and numbers have been observed in humans after treatment with other members of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Fenofibrate has been demonstrated to be devoid of mutagenic potential in the following tests: Ames, and micronucleus *in vivo*/rat. In addition, fenofibric acid, has been demonstrated to be devoid of mutagenic potential in the following tests: Ames, mouse lymphoma, chromosomal aberration and sister chromatid exchange in human lymphocytes, and unscheduled DNA synthesis in primary rat hepatocytes.

In a fertility study, rats were given oral dietary doses of fenofibrate. Males received doses for 61 days prior to mating and females for 15 days prior to mating through weaning, which resulted in no adverse effect on fertility at doses up to 300 mg/kg/day (~10 times the MRHD, based on mg/m^2 surface area comparisons).

14 CLINICAL STUDIES

14.1 Co-Administration Therapy with Statins

Efficacy and safety of Trilipix co-administered with statins were assessed in three 12-week, double-blind, controlled Phase 3 studies and one 52-week, long-term, open-label extension study in 2698 patients with mixed dyslipidemia. Patients were required to meet the following fasting lipid entry criteria: TG ≥ 150 mg/dL, and HDL-C < 40 mg/dL (males) and < 50 mg/dL (females), and LDL-C≥ 130 mg/dL. The three multicenter, randomized, double-blind, controlled studies had similar designs, differing primarily in the statin used for combination therapy/monotherapy. Each study compared the effects of 135 mg Trilipix co-administered with either a low dose or a moderate dose of statin with Trilipix monotherapy and statin monotherapy at the corresponding dose on CHD lipid risk factors. A smaller group of patients received a high dose of statin monotherapy. In study 1, patients received Trilipix co-administered with 10 mg or 20 mg rosuvastatin. In study 2, patients received Trilipix co-administered with 20 mg or 40 mg simvastatin. In study 3, patients received Trilipix co-administered with 20 mg or 40 mg atorvastatin.

Patients were enrolled for a total of approximately 22 weeks, consisting of a 6-week diet run-in/washout period, a 12-week treatment period, and a 30-day safety follow up period. Patients who completed the 12-week treatment period were eligible to participate in the 52-week long-term extension study. Of the 2698 randomized and treated subjects in the controlled studies, 51.6% were female and 48.4% were male; 92.6% of all subjects were White, 4.7% were Black, and 2.8% were of other races. Hispanics comprised 9.9% of the study population. Mean age was 54.9 years.

The primary efficacy endpoints for all three studies were mean percent changes from baseline to final value in HDL-C, TG, and LDL-C. For each statin dose co-administered with Trilipix, there were three primary comparisons. For HDL-C and TG, Trilipix co-administered with each statin dose was compared with statin monotherapy at the corresponding dose. For LDL-C, Trilipix co-administered with each statin dose was compared with Trilipix monotherapy. In order to declare combination therapy successful for a particular statin dose, all three primary comparisons were required to demonstrate superiority of the combination therapy over the corresponding monotherapy. The primary efficacy results were consistent in the three studies and were confirmed by the pooled analysis of the three studies. The results from the individual studies and the pooled analysis demonstrated that Trilipix co-administered with low-dose statins and moderate-dose statins was superior to the corresponding monotherapy. Statistically significant differences were observed for all three primary efficacy comparisons for both doses of combination therapy in all three double-blind, controlled studies as well as the pooled analysis.

In the pooled analysis, Trilipix co-administered with both low-dose statins and moderate-dose statins resulted in mean percent increases (18.1% and 17.5%) in HDL-C and mean percent decreases (-43.9% and -42.0%) in TG that were significantly greater than the corresponding dose of statin monotherapy (7.4% and 8.7% for HDL-C; -16.8% and -23.7% for TG). In addition, both doses of combination therapy resulted in mean percent decreases (-33.1% and -34.6%) in LDL-C that were significantly greater than Trilipix monotherapy (-5.1%). The results of the pooled analysis are described in Table 5.

Table 5. Mean Percent Change from Baseline to the Final Value in HDL-C, TG, and LDL-C (Pooled Double-Blind, Controlled Studies)

	Trilipix	**Low-Dose Statin**	**Trilipix + Low-Dose Statin**	**Between-group # (p-value)**	**Moderate-Dose Statin**	**Trilipix + Moderate-Dose Statin**	**Between-group # (p-value)**	**High-Dose Statin**
HDL-C (mg/dL)	(N = 420)	(N = 455)	(N = 423)		(N = 430)	(N = 422)		(N = 217)
BL mean	38.4	38.4	38.2		38.4	38.1		38.0
Mean % #	16.3%	7.4%	18.1%	10.7%[a] (< 0.001)	8.7%	17.5%	8.8%[a] (< 0.001)	7.9%
TG (mg/dL)	(N = 459)	(N = 477)	(N = 470)		(N = 472)	(N = 462)		(N = 235)
BL mean	280.7	286.1	282.1		287.9	286.1		282.5
Mean % #	-31.0%	-16.8%	-43.9%	-27.2%[a] (< 0.001)	-23.7%	-42.0%	-18.3%[a] (< 0.001)	-28.1%
LDL-C (mg/dL)	(N = 427)	(N = 463)	(N = 436)		(N = 439)	(N = 434)		(N = 225)
BL mean	158.4	153.8	155.7		158.0	156.4		156.1
Mean % #	-5.1%	-33.9%	-33.1%	-28.0%[b] (< 0.001)	-40.6%	-34.6%	-29.5%[b] (< 0.001)	-47.1%

[a] Combination therapy vs. corresponding statin monotherapy

[b] Combination therapy vs. Trilipix monotherapy

Low-dose statin = rosuvastatin 10 mg, simvastatin 20 mg, or atorvastatin 20 mg

Moderate-dose statin = rosuvastatin 20 mg, simvastatin 40 mg, or atorvastatin 40 mg

High-dose statin = rosuvastatin 40 mg, simvastatin 80 mg, or atorvastatin 80 mg

BL = Baseline

% # = Percent change from baseline to final value

Secondary efficacy endpoints in all three double-blind, controlled studies were percent changes in non-HDL-C (Trilipix co-administered with statin compared to Trilipix monotherapy and corresponding statin monotherapy), and percent changes in VLDL-C, Total-C, and Apo B (Trilipix co-administered with statin compared to corresponding statin monotherapy). Co-administration of Trilipix with statins resulted in the following changes in secondary parameters (Table 6).

Table 6. Percent Change from Baseline to the Final Value in Non-HDL-C, VLDL-C, Total-C, and Apo B (Pooled Double-Blind, Controlled Studies)

Secondary Endpoints	**Trilipix**	**Low-Dose Statin**	**Trilipix + Low-Dose Statin**	**Between-group #**	**Moderate-Dose Statin**	**Trilipix + Moderate-Dose Statin**	**Between-group #**	**High-Dose Statin**
Non HDL-C (mg/dL)	(N = 420)	(N = 454)	(N = 422)		(N = 431)	(N = 420)		(N = 217)
BL mean	222.5	217.6	219.9		222.4	218.9		220.2

Mean % #				-23.1%[a]			-24.8%[a]	
	-17.3%	-34.9%	-40.4%	-5.5%[b]	-42.4%	-42.0%	0.4%[b]	-47.3%
VLDL-C (mg/dL)	(N = 449)	(N = 463)	(N = 455)		(N = 458)	(N = 449)		(N = 232)
BL mean	65.0	66.0	65.5		67.8	64.5		66.1
Mean % #	-34.2%	-32.1%	-50.0%	-18.0%[b]	-38.9%	-51.2%	-12.3%[b]	-42.1%
Total-C (mg/dL)	(N = 459)	(N = 477)	(N = 469)		(N = 472)	(N = 462)		(N = 235)
BL mean	260.9	257.0	258.6		261.3	257.3		258.8
Mean % #	-12.4%	-28.7%	-31.5%	-2.8%[b]	-34.7%	-33.3%	1.4%[b]	-39.5%
Apo B (mg/dL)	(N = 455)	(N = 470)	(N = 465)		(N = 468)	(N = 455)		(N = 229)
BL mean	146.2	145.0	146.1		147.1	145.0		146.0
Mean % #	-15.6%	-31.1%	-36.3%	-5.2%[b]	-36.9%	-36.7%	0.2%[b]	-42.4%

[a] Trilipix + statin vs. Trilipix monotherapy

[b] Trilipix + statin vs. corresponding statin monotherapy

Low-dose statin = rosuvastatin 10 mg, simvastatin 20 mg, or atorvastatin 20 mg
Moderate-dose statin = rosuvastatin 20 mg, simvastatin 40 mg, or atorvastatin 40 mg
High-dose statin = rosuvastatin 40 mg, simvastatin 80 mg, or atorvastatin 80 mg
BL = Baseline
% # = Percent change from baseline to final value

A total of 1895 patients who completed 12 weeks of treatment in the double-blind, controlled studies were treated in the 52-week, long-term extension study. Patients received Trilipix co-administered with the moderate-dose of the statin that had been used in the double-blind, controlled study in which they were enrolled. Whether combination therapy was initiated during the double-blind, controlled studies or introduced during the long-term extension study, the treatment effect of combination therapy was observed within four weeks, and was sustained over the duration of treatment in the long-term study. A total of 568 patients completed 52 weeks of treatment with Trilipix co-administered with statins. Mean 52-week values and mean percent change from baseline (at time of enrollment in randomized controlled trials) were 91.7 mg/dL (-38.2%) for LDL-C, 47.3 mg/dL (+24.0%) for HDL-C, 135.5 mg/dL (-47.6%) for TG, 117.9 mg/dL (-45.7%) for non-HDL-C, 26.2 mg/dL (-53.1%) for VLDL-C, 165.2 mg/dL (-35.4%) for Total-C, and 81.4 mg/dL (-43.6%) for Apo B.

14.2 Hypertriglyceridemia

The effects of fenofibrate on serum triglycerides were studied in two randomized, double-blind, placebo-controlled clinical trials of 147 hypertriglyceridemic patients. Patients were treated for eight weeks under protocols that differed only in that one entered patients with baseline TG levels of 500 to 1500 mg/dL, and the other TG levels of 350 to 500 mg/dL. In patients with hypertriglyceridemia and normal cholesterolemia with or without hyperchylomicronemia, treatment with fenofibrate at dosages equivalent to 135 mg once daily of Trilipix decreased primarily VLDL-TG and VLDL-C. Treatment of patients with elevated TG often results in an increase of LDL-C (Table 7).

Table 7. Effects of Fenofibrate in Patients With Hypertriglyceridemia

Study 1	**Placebo**				**Fenofibrate**			
Baseline TG levels 350 to 499 mg/dL	**N**	**Baseline Mean (mg/dL)**	**Endpoint Mean (mg/dL)**	**Mean % Change**	**N**	**Baseline Mean (mg/dL)**	**Endpoint Mean (mg/dL)**	**Mean % Change**
Triglycerides	28	449	450	-0.5	27	432	223	-46.2*
VLDL Triglycerides	19	367	350	2.7	19	350	178	-44.1*
Total Cholesterol	28	255	261	2.8	27	252	227	-9.1*
HDL Cholesterol	28	35	36	4	27	34	40	19.6*

LDL Cholesterol	28	120	129	12	27	128	137	14.5
VLDL Cholesterol	27	99	99	5.8	27	92	46	-44.7*
Study 2	**Placebo**				**Fenofibrate**			
Baseline TG levels 500 to 1500 mg/dL	**N**	**Baseline Mean (mg/dL)**	**Endpoint Mean (mg/dL)**	**Mean % Change**	**N**	**Baseline Mean (mg/dL)**	**Endpoint Mean (mg/dL)**	**Mean % Change**
Triglycerides	44	710	750	7.2	48	726	308	-54.5*
VLDL Triglycerides	29	537	571	18.7	33	543	205	-50.6*
Total Cholesterol	44	272	271	0.4	48	261	223	-13.8*
HDL Cholesterol	44	27	28	5.0	48	30	36	22.9*
LDL Cholesterol	42	100	90	-4.2	45	103	131	45.0*
VLDL Cholesterol	42	137	142	11.0	45	126	54	-49.4*

* = $p < 0.05$ vs. Placebo

14.3 Primary Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia

The effects of fenofibrate at a dose equivalent to Trilipix 135 mg once daily were assessed from four randomized, placebo-controlled, double-blind, parallel-group studies including patients with the following mean baseline lipid values: Total-C 306.9 mg/dL; LDL-C 213.8 mg/dL; HDL-C 52.3 mg/dL; and triglycerides 191.0 mg/dL. Fenofibrate therapy lowered LDL-C, Total-C, and the LDL-C/HDL-C ratio. Fenofibrate therapy also lowered triglycerides and raised HDL-C (Table 8).

Table 8. Mean Percent Change in Lipid Parameters at End of Treatment†

Treatment Group	Total-C (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)	TG (mg/dL)
Pooled Cohort				
Mean baseline lipid values (n = 646)	306.9	213.8	52.3	191.0
All Fenofibrate (n = 361)	-18.7%*	-20.6%*	+11.0%*	-28.9%*
Placebo (n = 285)	-0.4%	-2.2%	+0.7%	+7.7%
Baseline LDL-C > 160 mg/dL and TG < 150 mg/dL				
Mean baseline lipid values (n = 334)	307.7	227.7	58.1	101.7
All Fenofibrate (n = 193)	-22.4%*	-31.4%*	+9.8%*	-23.5%*
Placebo (n = 141)	+0.2%	-2.2%	+2.6%	+11.7%
Baseline LDL-C > 160 mg/dL and TG ≥ 150 mg/dL				
Mean baseline lipid values (n = 242)	312.8	219.8	46.7	231.9
All Fenofibrate (n = 126)	-16.8%*	-20.1%*	+14.6%*	-35.9%*
Placebo (n = 116)	-3.0%	-6.6%	+2.3%	+0.9%

† Duration of study treatment was 3 to 6 months

* p = < 0.05 vs. Placebo

In a subset of the subjects, measurements of Apo B were conducted. Fenofibrate treatment significantly reduced Apo B from baseline to endpoint as compared with placebo (-25.1% vs. 2.4%, $p < 0.0001$, n = 213 and 143, respectively).

16 HOW SUPPLIED/STORAGE AND HANDLING

Trilipix (fenofibric acid) delayed release capsules are supplied in two dose strengths as follows:

- Trilipix 45 mg fenofibric acid delayed release capsules have a reddish-brown cap imprinted in white ink the Abbott "A" logo and a yellow body imprinted in black ink the number "45". Each hard gelatin capsule contains enteric coated white to off white bi-convex round mini-tablets. The delayed release capsules are available in bottles of 90 (NDC 0074-9642-90).

- Trilipix 135 mg fenofibric acid delayed release capsules have a blue cap imprinted in white ink the Abbott "A" logo and a yellow body imprinted in black ink the number "135". Each hard gelatin capsule contains enteric coated white to off white bi-convex round mini-tablets. The delayed release capsules are available in bottles of 90 (NDC 0074-9189-90).

Storage and Handling

Store Trilipix 45 and 135 mg delayed release capsules at 25°C (77°F); excursions permitted to 15°-30°C (59° to 86°F) [See USP controlled room temperature]. Keep out of the reach of children. Protect from moisture.

17 PATIENT COUNSELING INFORMATION

See Medication Guide (17.2)

17.1 Patient Counseling

Patients should be advised:

- of the potential benefits and risks of Trilipix.

- to read the Medication Guide before starting Trilipix therapy and to reread it each time the prescription is renewed.

- of medications that should not be taken in combination with Trilipix.

- to continue to follow an appropriate lipid-modifying diet while taking Trilipix.

- to take Trilipix once daily, without regard to food, at the prescribed dose, swallowing each capsule whole. If Trilipix is co-administered with a statin, they may be taken together.

- to return for routine monitoring.

- to inform their physician of all medications, supplements, and herbal preparations they are taking and any change to their medical condition. Patients should also be advised to inform their physicians prescribing a new medication that they are taking Trilipix.

- to inform their physician of any muscle pain, tenderness, or weakness; onset of abdominal pain; or any other new symptoms.

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17.2 Medication Guide

MEDICATION GUIDE

Trilipix

(try-lip-iks)

(fenofibric acid, delayed release capsules)

Read this Medication Guide before you start taking Trilipix and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about Trilipix?

Trilipix can be used with other cholesterol-lowering medicines called statins. Statins include:

- atorvastatin (Lipitor, Caduet)

- fluvastatin (Lescol, Lescol XL)

- lovastatin (Altoprev, Mevacor, Advicor)

- pravastatin (Pravachol)

- rosuvastatin (Crestor)

• simvastatin (Zocor, Simcor, Vytorin)

Statins can cause muscle pain, tenderness or weakness, which may be symptoms of a rare but serious muscle condition called rhabdomyolysis. In some cases rhabdomyolysis can cause kidney damage and death. The risk of rhabdomyolysis may be higher when Trilipix is given with statins. If you take a statin, tell your healthcare provider.
Other medicines or large amounts of grapefruit juice (more than a quart) may raise the levels of statins in your body, and could then raise the risk of muscle problems. Tell your healthcare provider if you are taking any medicines listed below.
• Heart medicine

• Stomach medicine

• Antibiotic

• Anti-fungal

• Cholesterol-lowering medicine

• Hormones

• HIV/AIDS medicine

• Antidepressant

• Immunosuppressant

• Anti-seizure medicine

Ask your healthcare provider or pharmacist for a list of these medicines, if you are not sure.
Tell your healthcare provider if you drink grapefruit juice.
What is Trilipix?
Trilipix is a prescription medicine used to treat cholesterol in the blood by lowering the total amount of triglycerides and LDL (bad) cholesterol, and increasing the HDL (good) cholesterol. You should be on a low fat and low cholesterol diet while you take Trilipix.
The safety and effectiveness of Trilipix in children is not known.
Who should not take Trilipix?
Do not take Trilipix if you:
• are allergic to fenofibric acid, or any of the ingredients in Trilipix. See the end of this Medication Guide for a list of all the ingredients in Trilipix.

• have severe kidney disease.

• have liver disease.

• have gallbladder disease.

• are a nursing mother.

Talk to your healthcare provider before you take Trilipix if you have any of these conditions.
What should I tell my healthcare provider before taking Trilipix?
Before taking Trilipix, tell your healthcare provider about all your medical conditions, including if you:
• are allergic to any medicines.

• have ever had kidney problems.

• have ever had liver problems.

• have ever had gallbladder problems.

• are pregnant or if you plan to become pregnant. It is not known if Trilipix will harm your unborn baby.

• are breastfeeding or plan to breastfeed. It is not known if Trilipix passes into your breast milk. You and your healthcare provider should decide if you will take Trilipix or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements.
Using Trilipix with certain other medicines can affect the way these medicines work and other medicines may affect how Trilipix works. In some cases, using Trilipix with other medicines can cause serious side effects.
Know all the medicines you take. Keep a list of them and show it to your healthcare provider when you get a new medicine.
It is especially important to tell your healthcare provider if you take any of the medicines mentioned in, "What is the most important information I should know about Trilipix?" or any of the medicines listed below:
- **anticoagulants**, also known as blood thinners (warfarin, Coumadin)
- **bile acid resins**
- **cyclosporine**

Ask your healthcare provider if you are not sure if your medicine is one of these.
How should I take Trilipix?
- You should be on a low fat and low cholesterol diet while you take Trilipix.
- Take Trilipix one time each day as prescribed by your healthcare provider.
- Take Trilipix with or without food.
- Swallow Trilipix capsules whole. Do not break, crush, dissolve, or chew Trilipix capsules before swallowing. If you cannot swallow Trilipix capsules whole, tell your healthcare provider, you may need a different medicine.
- If you take a medicine called a statin, you can take Trilipix and your statin at the same time of day.
- If you miss a dose of Trilipix, take it as soon as you remember. If it is almost time for your next dose, just skip the missed dose. Take the next dose at your regular time. If you are not sure about your dosing, call your healthcare provider. **Do not take more than one dose of Trilipix a day unless your healthcare provider tells you to.**
- If you take too much Trilipix, contact your healthcare provider or your local emergency department.
- Do not change your dose or stop Trilipix unless your healthcare provider tells you to.
- Your healthcare provider may do blood tests before you start taking Trilipix and during treatment. See your healthcare provider regularly to check your cholesterol and triglyceride levels and to check for side effects.

What are the possible side effects with Trilipix?
Trilipix may cause serious side effects, including:
- **muscle pain, tenderness, or weakness.** See "What is the most important information that I should know about Trilipix?"
- **tiredness and fever.**
- **abdominal pain, nausea, or vomiting.** These may be signs of inflammation (swelling) of the gallbladder or pancreas.

Call your healthcare provider right away if you have any of these serious side effects.
The most common side effects with Trilipix include:
- headache
- heartburn (indigestion)
- nausea
- muscle aches
- increases in muscle or liver enzymes that are measured by blood tests

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of Trilipix. For more information, ask your healthcare provider or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
How do I store Trilipix?
- Store Trilipix between 59° to 86° F (15° to 30° C).

• Protect Trilipix from moisture.

Keep Trilipix and all medicines out of the reach of children.

General information about the safe and effective use of Trilipix

Medicines are sometimes prescribed for conditions that are not mentioned in the Medication Guide. Do not use Trilipix for a condition for which it was not prescribed. Do not give Trilipix to other people, even if they have the same condition you have. It may harm them.

This Medication Guide summarizes the most important information about Trilipix. If you would like more information, talk to your healthcare provider. You can also ask your pharmacist or healthcare provider for information that is written for health professionals. For more information go to www.Trilipix.com or call 1-800-633-9110.

What are the ingredients in Trilipix?

Active Ingredient: Fenofibric acid

Inactive Ingredients: Hypromellose, povidone, water, hydroxylpropyl cellulose, colloidal silicon dioxide, sodium stearyl fumarate, methacrylic acid copolymer, talc, triethyl citrate, gelatin, titanium dioxide, and yellow iron oxide. Additionally, the 45 mg capsule shell contains black iron oxide and red iron oxide, and the 135 mg capsule shell contains FD&C Blue #2.

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

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